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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 10/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/032,281	WYRICK ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-11,15-26,28-43,45-59 and 61-86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-11,15-26,28-43,45-59 and 61-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. In the previous action, it was incorrectly noted that Applicant elected without traverse. Applicant did elect with traverse, but the traverse is not found persuasive since the argument is that there is no burden of search to examine both groups. In fact, there is a significant burden since different art and different search terms would be required for the search of the second group.

Claim Interpretation

2. Several of the terms in the claims lack specific definitions in the specification and are broadly interpreted. The term "intergenic" is interpreted as any region in the genome which is "between two genes" where a gene is an open reading frame. The term "microarray" is simply any substrate with which a nucleic acid can be hybridized. The term "consensus DNA binding region" in claim 21 does not structurally distinguish from a particular DNA binding region and is broadly read as any DNA binding region.

Response to Arguments – Claim interpretation

3. Applicant's arguments filed September 19, 2005 have been fully considered but they are not persuasive.

Applicant argues that "intergenic" would not include a transcribed region of a gene. This is simply factually not true. As shown by the attached web page from The Scientist (http://www.the-scientist.com/news/20040603/01) "Although it's becoming more apparent that the intergenic space between protein-coding genes—often referred to as "junk"—is actively transcribed and often produces non–protein-coding RNAs, the

role of these RNAs and their transcription is largely unknown." So the intergenic region can be transcribed. Consequently, the interpretation used for the rejection is consistent with the art recognized interpretation of the term.

Applicant then argues that a DNA microarray must represent an orderly arrangment of nucleic acids. Applicant points to no support for this interpretation. The term is not defined in the specification. MPEP 2111 notes "During patent examination, the pending claims must be "given their broadest reasonable interpretation consistent with the specification". Since the specification does not define the term "microarray", the term carries its full breadth. While it is clear that Applicant disagrees with the interpretation of the claim, there is no structural element of the claim which distinguishes the Orlando reference. When Applicant discusses the limitation of "each fragment at a specific, discrete location on the surface", this is not in the claims. The decision of the court in In re Bigio, 72 USPQ2d 1209 (Fed. Cir. 2004) strongly supports the breadth of interpretation. That court notes "Nevertheless, this court counsels the PTO to avoid the temptation to limit broad claim terms solely on the basis of specification passages."

Applicant then argues that "consensus DNA binding region" represents an "idealized sequence". This may be true, but since any DNA sequence is a "consensus" of itself, this limitation does not impose any specific structure on the claims. Therefore, any DNA sequence may be deemed at consensus sequence of itself.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 1-6, 8, 10, 11, 17-22, 39-43, 45, 48-53, 56-59, 61, 64-68, 71-76 and 78-84 are rejected under 35 U.S.C. 102(b) as being anticipated by Orlando et al (Methods (1997) 11:205-214).

Orlando teaches a method of claims 1, 10, 11 and 71 for identifying a region of a genome of a cell to which a protein of interest binds (see abstract) comprising the steps of:

a) crosslinking DNA binding proteins in the cell to genomic DNA of the cell, thereby producing DNA binding protein crosslinked to genomic DNA (see figure 1 and page 205-206, subheading "1. In vivo Formaldehyde fixation of cells"),

b) generating DNA fragments of the genomic DNA crosslinked to DNA binding protein in a), thereby producing a mixture comprising DNA fragments to which DNA binding protein is bound (see figure 1 and page 206, subheading "2. Chromatin solubilization by sonication"),

c) removing a DNA fragment to which the protein of interest is bound from the mixture produced in b) (see figure 1 and page 209, subheading "5. Immunoprecipitation of crosslinked chromatin"),

d) separating the DNA fragment identified in c) from the protein of interest (see figure 1 and page 210, subheading "6. Reversal of cross-links and DNA purification"),

e) amplifying the DNA fragment of d) (see figure 1 and page 210-211, subheading "8. Amplification of immunoprecipitated DNA by linker modified DNA PCR"),

f) combining the DNA fragment of e) with DNA comprising sequences complementary to intergenic regions of genomic DNA of the cell under conditions in which hybridization between the DNA fragments and a sequence complementary to an intergenic region of the genomic DNA occurs (see figure 1 and subheading "9. southern analysis and mapping of binding sites in DNA" where the figures 6 and 7 demonstrate that intergenic regions are on the blot as shown by the presence of probes such as probe 2206 which is between the ultrabithorax and abdominal-A genes),

g) identifying the one or more sequences complementary to the one or more intergenic regions of genomic DNA of f) to which the DNA fragment hybridizes whereby the region identified in g) is the region of the genome in the cell to which the protein of interest binds (see figure 1, page 211, column 2 and figures 6 and 7).

With regard to claims 1, 10, 11 and 71, Orlando teaches hybridization to a southern blot, which is a type of microarray as discussed above (see figure 6).

With regard to claims 2, 39, 56, 72, Orlando teaches the use of Drosophila melanogaster cells which are eukaryotic (see page 205, column 1).

With regard to claims 3, 40, Orlando teaches the use of DNA binding transcription factors (see page 213, column 2).

With regard to claims 4, 41, 57, 73, Orlando teaches crosslinking with formaldehyde (see page 205-206, subheading "1. In vivo Formaldehyde fixation of cells").

With regard to claims 5, 42, 58, 74, Orlando teaches the use of antibodies to bind the protein of interest (see page 209, subheading "5. Immunoprecipitation of crosslinked chromatin").

With regard to claims 6, 43, 59, 75, Orlando teaches the use of a ligation mediated PCR since the linkers must be ligated prior to PCR (see page 210-211, subheading "8. Amplification of immunoprecipitated DNA by linker modified DNA PCR").

With regard to claims 8, 45, 61, 76, Orlando teaches the use of a control (see figure 7, figure legend "The white bars indicate the fragments containing repetitive elements (M-repeats) that hybridized also with the control fraction").

With regard to claims 17, 48, 64, 79, Orlando teaches shearing the DNA to make fragments (see page 206, subheading "2. Chromatin solubilization by sonication").

With regard to claims 18-22, 49-53, 65-68, 80-84, Orlando teaches the entire upstream and downstream regions of the abdominal-A gene which inherently includes promoter and regulatory regions for abdominal-A and abdominal-B.

6. Claims 1-6, 8-11, 15-22, 25, 26, 28-36, 39-53, 56-59, 61-68 and 71-84 are rejected under 35 U.S.C. 102(e) as being anticipated by Mercola (U.S. Patent 6,410,233).

Mercola teaches a method of claims 1, 9, 10 and 11 for identifying a region of a genome of a cell to which a protein of interest binds (see abstract) comprising the steps of:

a) crosslinking DNA binding proteins in the cell to genomic DNA of the cell, thereby producing DNA binding protein crosslinked to genomic DNA (see figure 1),

b) generating DNA fragments of the genomic DNA crosslinked to DNA binding protein in a), thereby producing a mixture comprising DNA fragments to which DNA binding protein is bound (see figure 1),

c) removing a DNA fragment to which the protein of interest is bound from the mixture produced in b) (see figure 1),

d) separating the DNA fragment identified in c) from the protein of interest (see figure 1),

e) amplifying the DNA fragment of d) (see figure 1),

f) combining the DNA fragment of e) with DNA comprising sequences complementary to intergenic regions of genomic DNA of the cell under conditions in which hybridization between the DNA fragments and a sequence complementary to an intergenic region of the genomic DNA occurs (see figure 1),

g) identifying the one or more sequences complementary to the one or more intergenic regions of genomic DNA of f) to which the DNA fragment hybridizes whereby the region identified in g) is the region of the genome in the cell to which the protein of interest binds (see figure 1).

With regard to claims 1, 10, 11 and 71, Mercola teaches hybridization to cDNAs on a matrix (see figure 1), which is an express form of a microarray.

With regard to claims 9, 15, 16, 29-30, 46, 47, 62, 63, 77, 78, Mercola teaches the use of fluorescent labels such as Cy3 and Cy5 (see column 17, lines 60-65).

With regard to claims 2, 25, 39, 56, 72, Mercola teaches the use of cells which are eukaryotic (see column 11, line 23).

With regard to claims 3, 26, 40, Mercola teaches the use of DNA binding transcription factors (see column 11, line 6).

With regard to claims 4, 41, 57, 73, Mercola teaches crosslinking with formaldehyde (see figure 1).

With regard to claims 5, 42, 58, 74, Mercola teaches the use of antibodies to bind the protein of interest (see figure 1).

With regard to claims 6, 43, 59, 75, Mercola teaches the use of a ligation mediated PCR since the linkers must be ligated prior to PCR (see figure 1).

With regard to claims 8, 28, 45, 61, 76, Mercola teaches the use of a control (see column 19, lines 23-25).

With regard to claims 17, 31, 48, 64, 79, Mercola teaches shearing the DNA to make fragments (see figure 1).

With regard to claims 18-22, 49-53, 65-68, 80-84, Mercola teaches the analysis of the Egr-1 transcription factor control elements and genes (see example 1) where "EGR1 belongs to a group of proteins that are involved in the progress through G1

phase of the cell cycle (see

http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=eurekah.section.11998).

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 9, 15, 16, 25, 26, 28-36, 46, 47, 62, 63, 77 and 78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Orlando et al (Methods (1997) 11:205-214) in view of Hacia et al (Nucleic Acids Research (1998) 26(16):3865-3866).

Orlando teaches a method of claims 1, 10, 11 and 71 for identifying a region of a genome of a cell to which a protein of interest binds (see abstract) comprising the steps of:

a) crosslinking DNA binding proteins in the cell to genomic DNA of the cell, thereby producing DNA binding protein crosslinked to genomic DNA (see figure 1 and page 205-206, subheading "1. In vivo Formaldehyde fixation of cells"),

b) generating DNA fragments of the genomic DNA crosslinked to DNA binding protein in a), thereby producing a mixture comprising DNA fragments to which DNA binding protein is bound (see figure 1 and page 206, subheading "2. Chromatin solubilization by sonication"),

c) removing a DNA fragment to which the protein of interest is bound from the mixture produced in b) (see figure 1 and page 209, subheading "5. Immunoprecipitation of crosslinked chromatin"),

d) separating the DNA fragment identified in c) from the protein of interest (see figure 1 and page 210, subheading "6. Reversal of cross-links and DNA purification"),

e) amplifying the DNA fragment of d) (see figure 1 and page 210-211, subheading "8. Amplification of immunoprecipitated DNA by linker modified DNA PCR"),

f) combining the DNA fragment of e) with DNA comprising sequences complementary to intergenic regions of genomic DNA of the cell under conditions in which hybridization between the DNA fragments and a sequence complementary to an intergenic region of the genomic DNA occurs (see figure 1 and subheading "9. southern analysis and mapping of binding sites in DNA" where the figures 6 and 7 demonstrate that intergenic regions are on the blot as shown by the presence of probes such as probe 2206 which is between the ultrabithorax and abdominal-A genes),

g) identifying the one or more sequences complementary to the one or more intergenic regions of genomic DNA of f) to which the DNA fragment hybridizes whereby the region identified in g) is the region of the genome in the cell to which the protein of interest binds (see figure 1, page 211, column 2 and figures 6 and 7).

With regard to claims 1, 10, 11 and 71, Orlando teaches hybridization to a southern blot, which is a type of microarray as discussed above (see figure 6).

With regard to claims 2, 39, 56, 72, Orlando teaches the use of Drosophila melanogaster cells which are eukaryotic (see page 205, column 1).

With regard to claims 3, 40, Orlando teaches the use of DNA binding transcription factors (see page 213, column 2).

With regard to claims 4, 41, 57, 73, Orlando teaches crosslinking with formaldehyde (see page 205-206, subheading "1. In vivo Formaldehyde fixation of cells").

With regard to claims 5, 42, 58, 74, Orlando teaches the use of antibodies to bind the protein of interest (see page 209, subheading "5. Immunoprecipitation of crosslinked chromatin").

With regard to claims 6, 43, 59, 75, Orlando teaches the use of a ligation mediated PCR since the linkers must be ligated prior to PCR (see page 210-211, subheading "8. Amplification of immunoprecipitated DNA by linker modified DNA PCR").

With regard to claims 8, 45, 61, 76, Orlando teaches the use of a control (see figure 7, figure legend "The white bars indicate the fragments containing repetitive elements (M-repeats) that hybridized also with the control fraction").

With regard to claims 17, 48, 64, 79, Orlando teaches shearing the DNA to make fragments (see page 206, subheading "2. Chromatin solubilization by sonication").

With regard to claims 18-22, 49-53, 65-68, 80-86, Orlando teaches the entire upstream and downstream regions of the abdominal-A gene which inherently includes promoter and regulatory regions for abdominal-A and abdominal-B which also inherently bind cell cycle transcription factors such as GATA-1 (the abdA 5' upstream sequence includes TCCGCATCCGC, a GATA-1 site) which are cell cycle transcription factors (see figure 7 and attahed paper in Blood: 89(4):1182-1188 "These findings suggest that the regulation of EPOR mRNA level is mainly associated with GATA-1 gene expression in UT-7 cells undergoing proliferation, and that these serial events are under the control of, or related to, the cell cycle.").

Orlando does not teach the use of fluorescent labels, and in particular the use of Cy5.

Hacia teaches the use of a two label system where one of the labels is Cy5-phycoerythrin (see page 3865, column 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute the fluorescent Cy5 dye of Hacia into the detection method of Orlando since the use of fluorescent dyes permits replacement of the radioactive components used in Orlando and avoidance of radioactivity is desirable.

Further motivation to use the Cy5 dye of Hacia is provided by Hacia, who notes "An attractive aspect of this two color system is the minimal spectral overlap between the phycoerythrin and phycoerythrin-Cy5 dyes (see page 3866, column 2)." Hacia notes that "Two color analysis allows competitive hybridization between a reference standard and an unknown sample, improving the performance of the assay (see abstract)." So an ordinary practitioner, wishing to modify Orlando in order to solve Orlando's concern regarding background and specificity (see page 213, column 1, where Orlando is seriously concerned with background signal in the hybridization), would have been motivated to use the two color system of Hacia since the two color system would improve signal specificity and accuracy as taught by Hacia (see page 3866, column 2). Further motivation to use Cy5 is that minimal spectral overlap is imposed when this dye is used in combination with phycoerythrin as discussed by Hacia.

10. Claims 23, 24, 37, 38, 54, 55, 69, 70, 85 and 86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Orlando et al (Methods (1997) 11:205-214) in view of Hacia et al (Nucleic Acids Research (1998) 26(16):3865-3866) and further in view of Hallahan et al (J. Biol. Chem. (1995) 270(51):30303-9).

Orlando in view of Hacia teach the limitations of claims 1-11, 15-22, 25-36, 39-53 and 56-68 as discussed above.

In particular, Orlando clearly teaches that the method of analysis is generic, noting "We have substantially broadened the potential of the method by adapting it to the analysis of general transcription factors (see page 205, column 2)."

Orlando in view of Hacia do not teach the species of cell cycle transcription factors.

Hallahan teach the analysis of transcription factors that are associated with cell cycle and in particular, analyzed the G1, S and G2/M transitions (see page 30304, column 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to apply the method of Orlando in view of Hacia to any transcription factor, including cell cycle transcription factors such as those of Hallahan since Orlando notes "We have substantially broadened the potential of the method by adapting it to the analysis of general transcription factors (see page 205, column 2)." An ordinary practitioner would have been motivated to use the method of Orlando to study the transcription factors of Hallahan in order to determine where the transcription factors bind on the genomic DNA, in order to determine the higher order structure which controls gene transcription of these cell cycle factors of Hallahan.

11. Claims 23, 24, 37, 38, 54, 55, 69, 70, 85 and 86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mercola (U.S. Patent 6,410,233) in view of Hallahan et al (J. Biol. Chem. (1995) 270(51):30303-9).

Mercola teaches the limitations of claims 1-11, 15-22, 25-36, 39-53 and 56-68 as discussed above. Mercola teaches the analysis of the Egr-1 transcription factor control elements and genes (see example 1) where "EGR1 belongs to a group of proteins that are involved in the progress through G1 phase of the cell cycle (see http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=eurekah.section.11998).

Mercola does not teach the species of cell cycle transcription factors.

Hallahan teach the analysis of transcription factors that are associated with cell cycle and in particular, analyzed the G1, S and G2/M transitions (see page 30304, column 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to apply the method of Mercola to any transcription factor, particularly cell cycle transcription factors such as those of Hallahan since an ordinary practitioner would have been motivated to use the method of Mercola to study the transcription factors of Hallahan in order to determine where the transcription factors bind on the genomic DNA, in order to determine the higher order structure which controls gene transcription of these cell cycle factors of Hallahan.

Double Patenting

12. Claims 1-6, 8-11 and 15-26, 28-43, 45-59 and 61-86 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 6,410,243 in view of Hacia and further in view of Hallahan.

Claims 1-11 of U.S. Patent No. 6,410,243 teach a method of identifying a region of a genome of a living cell to which a protein of interest binds, comprising the steps of:

a) crosslinking DNA binding protein in the living cell to genomic DNA of the living cell, thereby producing DNA binding protein crosslinked to genomic DNA;

b) generating DNA fragments of the genomic DNA crosslinked to DNA binding protein in a), thereby producing a mixture comprising DNA fragments to which DNA binding protein is bound;

c) removing a DNA fragment to which the protein of interest is bound from the mixture produced in b);

d) separating the DNA fragment identified in c) from the protein of interest;

e) amplifying the DNA fragment of d);

f) combining the DNA fragment of e) with DNA comprising a sequence complementary to genomic DNA of the cell, under conditions in which hybridization between the DNA fragment and a region of the sequence complementary to genomic DNA occurs; and

g) identifying the region of the sequence complementary to genomic DNA of f) to which the DNA fragment hybridzes,

whereby the region identified in g) is the region of the genome in the cell to which the protein of interest binds.

2. The method of claim 1 wherein the cell is a eukaryotic cell.

3. The method of claim 1 wherein the protein of interest is selected from the group consisting of: a transcription factor and an oncogene.

4. The method of claim 1 wherein the DNA binding protein of the cell is crosslinked to the genome of the cell using formaldehyde.

5. The method of claim 1 wherein the DNA fragment of c) to which is bound the protein of interest is identified using an antibody which binds to the

protein of interest.

6. The method of claim 1 wherein the DNA fragment of e) is amplified using ligation-mediated polymerase chain reaction.

7. The method of claim 1 wherein the complement sequence of the genome of f) is a DNA microarray.

8. The method of claim 1 further comprising: h) comparing the region identified in g) with a control.

9. Teaches the method with the further step f) fluorescently labeling the DNA fragment of e) and i) comparing the fluorescence intensity measured in h) to the fluorescence intensity of a control, whereby fluorescence intensity in a region of the genome which is greater than the fluorescence intensity of the control in the region indicates the region of the genome in the cell to which the protein of interest binds.

11. teaches application of the method to a transcription factor which will bind to intergenic DNA.

The claims do not teach the use of Cy5 nor do they teach the use of cell cycle transcription factors.

Hacia teaches the use of a two label system where one of the labels is Cy5-phycoerythrin (see page 3865, column 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute the fluorescent Cy5 dye of Hacia into the detection method of claims 1-11 of U.S. Patent No. 6,410,243 since Hacia notes "An attractive aspect of this two color system is the minimal spectral overlap between the phycoerythrin and phycoerythrin-Cy5 dyes (see page 3866, column 2)." Hacia notes that "Two color analysis allows competitive hybridization between a reference standard and an unknown sample, improving the performance of the assay (see abstract)." So an ordinary practitioner, wishing to modify claims 1-11 of U.S. Patent No. 6,410,243 would have been motivated to use the two color system of Hacia since the two color system would improve signal specificity and accuracy as taught by Hacia (see page 3866, column 2). Further motivation to use Cy5 is that minimal spectral overlap is imposed when this dye is used in combination with phycoerythrin as discussed by Hacia.

Hallahan teach the analysis of transcription factors that are associated with cell cycle and in particular, analyzed the G1, S and G2/M transitions (see page 30304, column 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to apply the method of claims 1-11 of U.S. Patent No. 6,410,243 to any transcription factor, including cell cycle transcription factors such as those of Hallahan. An ordinary practitioner would have been motivated to use the method of claims 1-11 of U.S. Patent No. 6,410,243 to study the transcription factors of Hallahan in order to determine where the transcription factors bind on the genomic

DNA, in order to determine the higher order structure which controls gene transcription of these cell cycle factors of Hallahan.

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Response to Arguments – Prior art and Double Patenting

14. Applicant's arguments filed September 19, 2005 have been fully considered but they are not persuasive.

Applicant argues that Orlando does not anticipate the claims because of the term "microarray". As noted above, this term is interpreted broadly and Orlando still reads on the claims. Further, Orlando is applied to the new claims 71-86, either in 102 or 103.

Applicant argues that Mercola is deficient since Mercola discusses the use of cDNA arrays. In fact, figure 11 demonstrates that Mercola uses sequences outside the open reading frame. Only the underlined sequence consitutes an open reading frame. The remaining 5' sequence is a region between that open reading frame and the open reading frame of the next 5' gene. As discussed in the claim interpretation, the term "intergenic" is extremely broad and simply reads on any region between two genes.

The 5' sequence shown by Mercola is between two genes and therefore meets the limitation of the claims, when given their broadest reasonable interpretation.

With regard to Applicant's arguments on the 103 rejection of Orlando in view of Hacia, Applicant is essentially arguing that these are nonanalogous. Applicant specifically notes that "the southern analysis of Orlando et al. is not equivalent to the microarray analysis of Applicant's claimed invention". As discussed above, the term "microarray" is not limited to any specific format by Applicant in the specification. As noted above, there is no structural element of the claim which distinguishes the Orlando reference. When Applicant discusses the limitation of "each fragment at a specific, discrete location on the surface", this is not in the claims. The decision of the court in In re Bigio, 72 USPQ2d 1209 (Fed. Cir. 2004) strongly supports the breadth of interpretation. That court notes "Nevertheless, this court counsels the PTO to avoid the temptation to limit broad claim terms solely on the basis of specification passages."

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, specific motivation is provided in the rejection, which notes "It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute the fluorescent Cy5 dye of Hacia into the detection method of Orlando since the use of fluorescent dyes permits replacement of the radioactive components used in Orlando and avoidance of radioactivity is desirable. Further motivation to use the Cy5 dye of Hacia is provided by Hacia, who notes "An attractive aspect of this two color system is the minimal spectral overlap between the phycoerythrin and phycoerythrin-Cy5 dyes (see page 3866, column 2)." Hacia notes that "Two color analysis allows competitive hybridization between a reference standard and an unknown sample, improving the performance of the assay (see abstract)." So an ordinary practitioner, wishing to modify Orlando in order to solve Orlando's concern regarding background and specificity (see page 213, column 1, where Orlando is seriously concerned with background signal in the hybridization), would have been motivated to use the two color system of Hacia since the two color system would improve signal specificity and accuracy as taught by Hacia (see page 3866, column 2). Further motivation to use Cy5

is that minimal spectral overlap is imposed when this dye is used in combination with phycoerythrin as discussed by Hàcia."

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Conclusion

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey Fredman
Primary Examiner
Art Unit 1637

7/30/05